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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 05-AUG-2005

SUBJECT: PP#s: 8F4953, 0F6155, 9E5076, and 6F4748. Difenoconazole in/on Barley, Cotton, Sweet Corn, and Imported Grapes and Pome Fruit. **Health Effects Division (HED) Risk Assessment**. DP#s: 319944, 319946, 319947, and 319949. PC Code: 128847. Decision#s: 301882, 352038, 302952, and 300882.

FROM: Guruva Reddy, D.V.M., Ph.D., Veterinary Medical Officer
Sarah J. Levy, M.S., Chemist
Mark Dow, Ph.D., Biologist
Registration Action Branch 1 (RAB1)/HED (7509C)

THROUGH: P.V. Shah, Ph.D., Branch Senior Scientist
RAB1/HED (7509C)

TO: Cynthia Giles-Parker/John Bazuin (PM Team 22)
Registration Division (RD; 7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered and proposed uses of difenoconazole (1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4-triazole). A summary of findings is provided in this document. The risk assessment was provided by Guruva Reddy and Sarah Levy of RAB1; the hazard characterization was provided by Guruva Reddy; the residue chemistry review and dietary exposure assessment were provided by Sarah Levy; the occupational/residential exposure and risk assessment was provided by Mark Dow of RAB1; and the drinking water assessment was provided by Marie Janson, Alex Clem, and James Hetrick of the Environmental Fate and Effects Division (EFED).

NOTE: HED completed a Section 3 risk assessment for the use of difenoconazole in/on canola (Memo, Levy, *et al.*, 23-NOV-1999; DP# 258774). This document contains only those aspects of the risk assessment which are affected by the addition of the proposed difenoconazole uses.

Recommendation for Tolerances and Registration

Provided revised Sections B and F are submitted, the toxicological and residue chemistry databases, as well as the aggregate risk assessments, support conditional registration of the requested new uses and establishment of the following permanent tolerances for residues of difenoconazole *per se* as follows:

Barley, hay	0.05 ppm
Barley, straw	0.05 ppm
Barley, forage	0.05 ppm
Cotton, undelinted seed	0.05 ppm
Cotton, gin byproducts	0.05 ppm
Corn, sweet, forage	0.01 ppm
Corn, sweet, stover	0.01 ppm
Corn, sweet, kernel plus cob with husks removed	0.01 ppm
Grape	0.10 ppm
Fruit, pome, group 11	0.10 ppm

HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following residue chemistry data:

- Storage stability data on the processed commodities of apples (wet pomace and juice) and grapes (raisin and juice) are requested. The requested storage stability data should reflect the longest storage intervals reported in the respective processing studies (*i.e.*, 17.5 months for apples, 14.2 months for grape juice and 4.2 months for raisins).

- The confirmatory method has been determined to be suitable for tolerance enforcement once the revisions recommended by the Analytical Chemistry Laboratory (ACL) are incorporated.

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1.0 EXECUTIVE SUMMARY

Difenoconazole is a broad-spectrum fungicide with registered seed treatment uses on cereal grains and canola grown in the U.S. Difenoconazole tolerances have been established in 40 CFR §180.475 for plant and livestock commodities and are expressed in terms of difenoconazole *per se*. Syngenta has petitioned the Agency to establish tolerances resulting from foliar uses of difenoconazole on grapes and pome fruits grown in Australia, Chile, France, Germany, New Zealand, South Africa, and Switzerland and tolerances on sweet and pop corn and cotton grown in the U.S. There are no proposed or existing residential uses for difenoconazole.

Hazard Assessment

The toxicological database for difenoconazole is adequate to support Section 3 registration and permanent tolerances. There are no toxicology data gaps.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not considered to be an eye or skin irritant and is not a sensitizer. It is not neurotoxic or mutagenic. It is not a developmental or reproductive toxicant. Chronic effects in the rat study are seen as cumulative decreases in body weight gains. Evidence for carcinogenicity was seen in only one species, mice, where liver tumors were induced at doses which were considered to be excessively high for carcinogenicity testing. No evidence of carcinogenicity was seen in rats.

Chronic feeding studies in mice showed decreased body-weight gains in male and female mice at termination. Treatment-related non-neoplastic lesions were confined to the liver and were supported by the clinical chemistry data at a level of 300 ppm (46.29 and 57.79 mg/kg/day for males and females respectively). Liver tumors were observed in mice at 300 ppm and higher; however, based on the excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at the two lower doses of 10 and 30 ppm and the absence of genotoxic effects, HED's Cancer Peer Review Committee (CPRC) recommended for a cancer classification of C (**possible human carcinogen**). A margin of exposure (MOE) approach in risk assessment was advocated by the CPRC utilizing the no-observable-adverse-effects-level (NOAEL) of **30** ppm (**4.7** and **5.6** mg/kg/day in males and females respectively) and the lowest-observable-adverse-effects-level (LOAEL) of **300** ppm (**46.3** and **57.8** mg/kg/day in males and females respectively) from the mouse study using only those biological endpoints which were related to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis) (Memo, Jess Rowland and Esther Rinde, 27-JUL-1994).

For purposes of this action, HED recently reviewed the 27-JUL-1994 CPRC report on difenoconazole and the supporting data-evaluation records (DERs). The decision was to classify difenoconazole as a category C (possible human carcinogen) using a MOE approach based on both tumors and non-tumorgenic endpoints from the mouse cancer study. The NOAEL of 4.7 mg/kg/day from the mouse cancer study was recommended for use as the endpoint for cancer risk assessment. At the next dose of 46.3 mg/kg, there were increases in benign liver tumors in males and liver necrosis and liver hypertrophy.

It is clear that, by today's standards, there were not sufficient mode-of-action data to show that a MOE risk assessment could be supported. During that time in the 1990's, the CPRC was considering various options to the default low-dose linear risk assessments. Sometimes, a MOE risk assessment was recommended based both on tumors and tumor precursors from the cancer study and the 90-day subchronic study, even in the absence of any mode-of-action data. Based on today's Agency cancer guidelines, HED would need plausible biological mode-of-action data to consider non-linear or threshold methods of risk assessment.

In the case of difenoconzole, the carcinogenic effects occurred only at excessive doses in the mouse. At the dose of 300 ppm in males (which was considered adequate and not excessive), there was an increase in benign liver tumors but the level of significance did not reach the statistical significance ($p < 0.01$) needed for these commonly-occurring tumors.

HED concluded that difenoconazole is a very weak carcinogen, showing effects only at excessive doses. In retrospect, the CPRC should have classified this pesticide as a category C with no linear quantification of cancer risk. The chronic reference dose (RfD), based on borderline liver effects in male rats at 24.1 mg/kg and a NOAEL of 0.96 mg/kg, would certainly be protective of any carcinogenic effects seen in the mouse.

Dose-Response Assessment

On 08-SEP-1998, HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of difenoconazole and re-assessed the RfD established in 1994, as well as the toxicological endpoints for the dietary and occupational exposure risk assessments that were selected in 1994. At this meeting, the HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to difenoconazole as required by the Food Quality Protection Act (FQPA) of 1996 (HED Doc. No. 012873, 25-SEP-1998). Shortly thereafter, the HED FQPA Safety Factor Committee (SFC) met on 19-OCT-1998 and recommended that the default 10x FQPA Safety Factor (SF) be reduced to 1x when assessing acute and chronic dietary exposures (HED Doc. No. 012924, 28-OCT-1998). This decision is supported by recent OPP Guidance ("Determination of the Appropriate FQPA SF(s) in Tolerance Assessment," 2002), which recommends reduction of the 10x SF in cases where the degree of concern for susceptibility to infants and children is low, residual uncertainties in the database are low, and the overall confidence in the risk assessment is high. Difenoconazole is neither a developmental nor a reproductive toxicant; therefore, the degree of concern for pre- and postnatal toxicity is low. Moreover, there are no residual uncertainties in the toxicology database. The toxicological doses relevant to this assessment are summarized below.

Acute dietary (females 13 - 49 years old)	NOAEL = 25 mg/kg/day	acute Rfd and acute population-adjusted dose (PAD) = 0.25 mg/kg/day
Chronic dietary	NOAEL = 0.96 mg/kg/day	chronic Rfd and cPAD = 0.01 mg/kg/day
Short-term dermal	oral NOAEL = 25 mg/kg/day	Target MOE ≥ 100 (occupational)
Intermediate-term dermal	oral NOAEL = 1.25 mg/kg/day	Target MOE ≥ 100 (occupational)

Occupational Exposure and Risk Assessments

The occupational exposure assessment addresses the use of Dividend® (EPA Reg. # 100-740), which contains 32.8% difenoconazole. Difenoconazole is a fungicide used as a systemic seed dressing to control certain seed-borne and soil-borne diseases. The product label specifies a maximum application rate of 0.0305 pounds of difenoconazole per 100 pounds of seed.

Based on the proposed barley, cotton, and sweet corn seed treatment uses of difenoconazole, the potential for occupational exposures exists. There are no residential uses. For this action, occupational exposure to difenoconazole is limited to the workers involved in the commercial seed treatment. The label specifies that this product is only for use in commercial seed treatment plants. In the seed-treatment setting, most highly-exposed occupational pesticides handlers in this case are: mixer/operator, bagger, and bag sewer. Therefore, exposure calculations were done for the mixer/operator, bagger, and bag-sewer scenario only. All risk estimates for the mixer/operator, bagger, and bag-sewer scenarios are well below HED's level of concern.

The HIARC determined that inhalation risk assessments are not required since inhalation toxicological end-points of concern were not identified for this route of exposure. Only short- and intermediate-term dermal exposure are expected for the seed treatment, given durations. Long-term exposure is not expected for use of difenoconazole in seed treatment plants.

Handler exposures are not expected to be chronic exposures; therefore, a cancer risk assessment is not necessary for this action.

There are no personal-protective equipment (PPE) directions on the label. There is a restricted entry interval (REI) of 12 hours (to fields planted with treated seed).

Drinking Water

Since HED does not have ground or surface water monitoring data to calculate quantitative aggregate exposure, estimates of difenoconazole levels in surface and ground water were made using computer modeling. Tier I estimated drinking water concentrations (EDWCs) were provided for both surface water (FQPA Index Reservoir Screening Tool (FIRST)) and groundwater (Screening Concentration in Ground Water (SCI-GROW)) by EFED (Memo, M. Janson, 02-MAY-2005; DP# 307166). The estimated average concentration of difenoconazole in ground water is **0.00084 ppb** (to be used for acute and chronic risk assessments). The estimated maximum and average concentrations of difenoconazole in surface water are **0.60 ppb** and **0.14 ppb**, respectively (to be used for acute and chronic risk assessments, respectively). Since the models are not specifically designed to estimate concentrations of pesticides used for seed treatment, there are uncertainties in their predictive potential. However, these uncertainties are not expected to substantially decrease the conservativeness of Tier I modeling results. Drinking water was incorporated directly into the dietary assessment.

Dietary Exposure Estimates

The following dietary exposure risk assessments were conducted for the existing uses and proposed new uses of difenoconazole: acute (for females 13-49 years old only) and chronic (for the U.S. population and all subgroups). A cancer dietary assessment was not conducted for difenoconazole because the cancer NOAEL is higher than the chronic RfD; therefore, the chronic dietary risk estimate is more protective.

The Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03) model) was used, which incorporates consumption data from the United States Department of Agriculture's (USDA) Continuing Surveys of Food Intake by Individuals (CSFII), 1994-1996 and 1998. No monitoring data from USDA's Pesticide Data Program (PDP) or the Food and Drug Administration's (FDA) Surveillance Monitoring Program were available for difenoconazole.

The acute analysis assumed tolerance-level residues, 100% crop treated (CT), DEEM™ (ver. 7.76) default processing factors, and modeled water concentrations for all registered and proposed commodities. The resulting acute food exposure estimates were less than HED's level of concern (<100% aPAD) at the 95th percentile (≤ 1.0% acute population-adjusted dose (aPAD) for females 13-49 years old). The chronic analysis assumed tolerance-level residues for all proposed commodities, anticipated residues (ARs) previously calculated for the registered commodities and 100% CT, DEEM™ (ver. 7.76) default processing factors, and modeled water concentrations for all commodities (partially refined, Tier 2 analysis). The resulting chronic food exposure estimates were less than HED's level of concern (<100% cPAD). Specifically, children 1-2 years old were the most highly-exposed population subgroup (≤ 16% cPAD).

Exposure Scenarios and Risk Conclusions

Including all existing and proposed uses, human-health risk assessments have been conducted for the following exposure scenarios: acute and chronic dietary exposures (food + water). **All aggregate exposure and risk estimates are below HED's level of concern.** Because there are no uses of difenoconazole that could result in residential exposures, this aggregate risk assessment takes into consideration dietary food + water exposure only.

Recommendation for Tolerances and Registration

Provided revised Sections B and F are submitted, the toxicological and residue chemistry databases, as well as the aggregate risk assessments, support conditional registration of the requested new uses and establishment of the following permanent tolerances for residues of difenoconazole *per se* as follows:

Barley, hay	0.05 ppm
Barley, straw	0.05 ppm
Barley, forage	0.05 ppm
Cotton, undelinted seed	0.05 ppm
Cotton, gin byproducts	0.05 ppm
Corn, sweet, forage	0.01 ppm
Corn, sweet, stover	0.01 ppm
Corn, sweet, kernel plus cob with husks removed	0.01 ppm
Grape	0.10 ppm
Fruit, pome, group 11	0.10 ppm

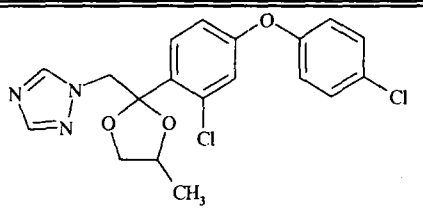
HED recommends that conversion of conditional registration to unconditional registration may be considered upon submission of the following residue chemistry data:

- Storage stability data on the processed commodities of apples (wet pomace and juice) and grapes (raisin and juice) are requested. The requested storage stability data should reflect the longest storage intervals reported in the respective processing studies (*i.e.*, 17.5 months for apples, 14.2 months for grape juice and 4.2 months for raisins).

- The confirmatory method has been determined to be suitable for tolerance enforcement once the revisions recommended by ACL are incorporated.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Test Compound Nomenclature for Difenoconazole.

Chemical structure	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	*cis-trans*-3-chloro-4-[4-methyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]phenyl 4-chlorophenyl ether
CAS name	1-[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4-triazole
CAS registry number	119446-68-3
End-use product (EP)	U.S. Registered Products: EPA Reg. Nos. 100-740, 100-814, 100-826, 100-885, 100-935, 100-973, and 100-1141.

Physicochemical Properties of the Technical Grade Test Compound.

Parameter	Value	Reference
Melting point/range	78.6°C	PP#2E4051; R. Lascola, 22-OCT-1992; DP#s: 172067 and 178394
pH	6-8 at 20°C (saturated solution)	
Density	1.37 g/cm^3 at 20°C	
Water solubility	3.3 ppm at 20°C	
Solvent solubility	g/100 mL at 25°C: n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10^{-10} mm Hg at 25°C	
Dissociation constant, pK_a	<0	
Octanol/water partition coefficient, Log(K_{ow})	4.2 at 25°C	
UV/visible absorption spectrum	Not available	

3.0 HAZARD CHARACTERIZATION

A detailed hazard characterization for difenoconazole is presented in HED's previous risk assessment (Memo, S. Levy *et al.*, 23-NOV-1999; DP# 258774). The doses and toxicological endpoints selected for various exposure scenarios applicable to this risk assessment are summarized in Table 1.

Table 1. Summary of Toxicological Doses and Endpoints of Difenoconazole.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Acute Dietary (females 13-49 years old)	NOAEL = 25 mg/kg/day UF = 100 **aRfD** = 0.25 mg/kg/day	FQPA SF = 1x **aPAD** = aRfD/FQPA SF = 0.25 mg/kg/day	**Developmental Rabbit** -post-implantation loss, increased resorptions per doe, decreased fetal body weight
Acute Dietary (General population including infants and children)	An endpoint of concern attributable to a single exposure (dose) for the general population was not identified from the oral toxicity studies including the rat and rabbit developmental toxicity studies.		
Chronic Dietary (all populations)	NOAEL = 0.96 mg/kg/day UF = 100 **cRfD** = 0.01 mg/kg/day	FQPA SF = 1x **cPAD** = cRfD/FQPA SF = 0.01 mg/kg/day	**Chronic/Onco Rat** -cumulative decreases in body weight gains
Short-Term Dermal[a] (1-30 days)	oral NOAEL = 25 mg/kg/day	Residential LOC for MOE = 100	**Developmental Rabbit** post-implantation loss, increased resorptions per doe, decreased body weight
Intermediate-Term Dermal[a] (1-6 months)	oral NOAEL=1.25 mg/kg/day	Residential LOC for MOE = 100	**2-Generation Reproduction Rat** -based on decreased pup weight on day 21
Inhalation (Any time period)	None	Based on the low acute toxicity [Toxicity Category IV] , the application rate, the application method, and the number of applications, there is minimal concern for potential inhalation exposure/risk. This risk assessment is not required.	

[a] The HIARC estimated a dermal-absorption factor of 75% based on the LOAEL established for the same endpoint in the oral developmental toxicity study in rabbits and the 21-day dermal toxicity study in rabbits.

3.1 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program

include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, difenoconazole may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT

residue chemistry summary - Memo, S. Levy, 03-AUG-2005; DP#307059
dietary exposure analysis - Memo, S. Levy, 03-AUG-2005; DP#319943
drinking water summary - EFED Memo, M. Janson, 02-MAY-2005; DP#307166

4.1 Summary of Registered Uses

U.S.: In the U.S., difenoconazole is currently registered for seed treatment to control seed-borne and soil-borne diseases of wheat and canola. Special Local Need (SLN) registrations exist for seed treatment of spring barley as well as Section 18 registration on sweet corn. According to the Agency's OPPIN database, end-use products containing difenoconazole as the active ingredient are sold in this country under the trade names Dividend®, Dividend® Extreme, Dividend® WS, Dividend® XL, Dividend® XL RTA, Helix®, and Helix® XTRA.

Difenoconazole tolerances have been established in 40 CFR §180.475. Tolerances for plant and livestock commodities are expressed in terms of difenoconazole *per se*. The established tolerances for plant commodities range from 0.01 ppm (canola, seed) to 0.2 ppm (imported bananas). Tolerances for milk, eggs, the fat, meat, and meat byproducts of cattle, goat, hog, horse, and sheep, and the fat, meat, and meat byproducts of poultry range from 0.01 to 0.05 ppm. Time-limited tolerances, with an expiration date of 31-DEC-2005, are established for sweet corn commodities at 0.1 ppm each to cover residues resulting from a Section 18 registration.

Import: Difenoconazole is currently registered for foliar uses on grapes in France and Switzerland, and proposed for use in Chile and South Africa. Difenoconazole is also currently registered for foliar uses on pome fruits in Australia, France, New Zealand, South Africa, and Switzerland, and proposed for registration in Chile and Germany.

4.2 Summary of Proposed Uses

Syngenta has petitioned the Agency to establish tolerances resulting from foliar uses of difenoconazole on imported grapes and pome fruits grown in Australia, Chile, France, Germany, New Zealand, South Africa, and Switzerland and domestic tolerances on sweet/pop corn and cotton.

The petitioner has provided the Agency copies of foreign labels with English translations. A list of difenoconazole end-use products (EPs), for which labels were provided as part of this action request, is presented in Table 2. A summary of proposed/registered use patterns on grapes, pome fruits, sweet/pop corn, and cotton is listed in Table 3.

Difenoconazole is currently registered for foliar uses on grapes in France and Switzerland, and proposed for registration in Chile and South Africa. Product use rates range 30-50 g ai/ha/application (0.027-0.045 lb ai/A/application) with a maximum of 3 or 4 applications depending on the country of use. Label pre-harvest intervals (PHIs) range 28-60 days or are "determined by stage of growth at last application."

Difenoconazole is currently registered for foliar uses on pome fruits in Australia, France, New Zealand, South Africa, and Switzerland. It is also proposed for registration in Chile and Germany. Product use rates range 37.5-87.5 g ai/ha/application (0.033-0.078 lb ai/A/application) with a maximum of 4 or 6 applications depending on the country of use. Label PHIs range 14-35 days.

The submitted labels contain information pertaining to the maximum single application rate, the maximum seasonal rate per growing season, application timing (as it relates to plant growth stage), retreatment interval (RTI), application tank-mix preparation, volume of spray mix per unit area, and the PHI. The application rates in the translated labels were, however, expressed in terms of "l/ha" or "ml/hl." The study reviewers were unable to convert these application rates to lb ai/A (or kg ai/ha) because information pertaining to the product density of liquid formulation was not available. The petitioner, however, calculated the rates in terms of "lb ai/A" in its summary documents. The application rates listed in Table 2 were copied from MRIDs 44785101 (grape summary document) and 44785102 (pome fruit summary document).

Table 2. List of Difenoconazole EPs Which May be Used on Grapes and/or Pome Fruits Grown in Foreign Countries.

Trade Name	a.i. in Formulation	Formulation Type[1]	Target Crops	Target Pests	Label Version
Score® 250 EC	2.08 lb/gal (250 g/L) difenoconazole	EC	Pome fruits (apples and pears); and grapes	Scab (*Venturia* spp) in apples and pears, and powdery mildew (*Podosphaera leucotricha*), and moldy core or black rot (*Alternaria alternata*) in apples; powdery mildew (*Uncinula necalor*) in grapes.	Chile Label dated 7/30/98
			Apples and pears; and table and wine grapes	Scab in apple and pear; powdery mildew (in grapes	South Africa Label Reg. No. L5132 dated 7/28/97 &4/30/98
			Apple, pear, quince, and Nashi trees; and grape vines	Scab for apples and pears; powdery mildew, black rot, and red fire for vines.	France Label EMB 30004, Ref. 825468
Slick® 250 EC	2.08 lb/gal (250 g/L) difenoconazole	EC	Grape vines	Red fire (*Pseudopeziza tracheiphila*), powdery mildew (*Uncinula necalor*), and black rot (*Guignardia bidwellii*)	Switzerland Label dated 8/6/97
Bogard® 100 WG	10% difenoconazole	WG	Apples and pears	Black spot (apple and pear scab; *Venturia inaequalis and Venturia pirina*)	Australia Label dated 10/27/98
Score® 10 WG	10% difenoconazole	WG	Apples and pears	Black spot in apples and pears, and powdery mildew in apples.	New Zealand Label
Score® Top 20 WG	14% difenoconazole 6% penconazole	WG	Pome fruit	Scab (*Venturia inaequalis*)	Germany Label dated 12/18/97
			Pome fruit	Scab (*Venturia inaequalis and Venturia pirina*), powdery mildew (*Podosphaera leucotricha*), blossom and branch brown rot, and Cluster cup rust (secondary effect)	Switzerland Label OFSP/BAG T No. 9206-4

Table 3. Summary of Directions for Use of Difenoconazole.

Trade Name	Application Timing; Type; and Equipment	Max. Applic. Rate[1] lb ai/A (g ai/ha)	Max. No. Applic. per Season	Max.[2] Seasonal Applic. Rate lb ai/A (g ai/ha)	PHI (days)	Use Directions and Limitations
			Grape			
Score® 250 EC (Chile)	Foliar; Broadcast; Equipment type not specified	0.045 (50)	3	0.134 (150)	60	Applications may be made to shoots 10-15 cm size onwards (5 leaves to inflorescence stage). Use lower rates at 14-21 day intervals or higher rates at 21-35 day intervals.
Score® 250 EC (France)	Foliar; Broadcast; All types of spray apparatus	0.027 (30)	4	0.107 (120)	Not specified	Applications may be made at 14 day intervals; shorter RTIs (10-12 days) may be used if disease is severe. PHI is determined by stage of growth at last application.
Score® 250 EC (South Africa)	Foliar; Broadcast; Ground and aerial	wine grapes: 0.027 (30) table grapes: 0.032 (36)	4	0.107 (120) 0.128 (144)	28	For wine grapes increase spray volume progressively from 250 L/ha to reach 1,000 L/ha at peaberry stage and repeat application (14-day intervals) throughout the rest of the season. For table grapes increase spray volume progressively from 500 L/ha to reach 1,200 L/ha. Last application made should be no later than bunch closure (berry touch completed).
Slick® 250 EC (Switzerland)	Foliar; Broadcast; Equipment type not specified	0.027 (30)	4	0.107 (120)	Not specified	Applications may be made pre-blossom up to first post-blossom. Tank mix with 0.1% Folpet DG to control red fire disease. PHI is determined by stage of growth at last application.
			Pome fruit			
Score® 250 EC (Chile)	Foliar; Broadcast; Equipment type not specified	0.045 (50)	4	0.178 (200)	28	Application rate is based on typical 2,000 L/ha spray volume; for orchards requiring spray volume <2,000 L/ha, the product must be concentrated proportionally. Applications to pome fruits from green tip stage may be made at 7-10 day intervals, and from petal fall onwards at 10-14 day intervals.

Table 3. Summary of Directions for Use of Difenoconazole.

Trade Name	Application Timing; Type; and Equipment	Max. Applic. Rate[1] lb ai/A (g ai/ha)	Max. No. Applic. per Season	Max.[2] Seasonal Applic. Rate lb ai/A (g ai/ha)	PHI (days)	Use Directions and Limitations
Score® 250 EC (France)	Foliar; Broadcast; All types of spray apparatus	0.033 (37.5)	5	0.167 (187.5)	30	Application rate is based on typical 1,000 L/ha spray volume. Applications may be made from stage C-C3 with 14 day intervals; shorter RTIs may be used if disease is severe.
Score® 250 EC (South Africa)	Foliar; Broadcast; Ground and aerial	0.045 (50)	4	0.178 (200)	14	Application rate is based on typical 2,000 L/ha (high vol.) spray volume; when low volume spray is used, the product must be concentrated properly (4x). Applications to pome fruits from green tip and throughout pre-blossom may be made at 7 day intervals, and during post-blossom at 10-14 day intervals. The label specifies that the product be applied as a tank mix with Kaptan Flo (Captan) or other suitable broad spectrum contact fungicides at 50-75% of the registered dose.
Bogard® 100 WG (Australia)	Foliar; Broadcast; Equipment type not specified	Alone (prior to petal fall): 0.062 (70) Tank Mix (post petal fall): 0.078 (87.5)	6 (max 4 alone)	0.406 (455)	28	Applications may be made by dilute (high volume) spraying to run-off or by concentrate (low volume) spraying; the same concentration is used for dilute or concentrate sprays. Dilute application rate is based on typical 2,000 L/ha spray volume prior to petal fall and 3500 L/ha (maximum) after petal fall due to increased foliage. Repeat applications at 7-10 day intervals until full petal fall; after petal fall apply only as a tank mix at 14-21 day intervals. Recommended tank mix at lower rate 2.5 g ai/100 L dilute or 50-87.5 g ai/ha concentrate) with a registered protectant Scab fungicide (at full registered rate).[3]

Table 3. Summary of Directions for Use of Difenoconazole.

Trade Name	Application Timing; Type; and Equipment	Max. Applic. Rate[1] lb ai/A (g ai/ha)	Max. No. Applic. per Season	Max.[2] Seasonal Applic. Rate lb ai/A (g ai/ha)	PHI (days)	Use Directions and Limitations
Score® 10 WG (New Zealand)	Foliar; Broadcast; Equipment type not specified	0.045 (50)	4 (6 with extreme disease pressure)	0.268 (300)	35	Applications may be made by dilute (high volume) spraying without excessive run-off or by concentrate (low volume) spraying; the same concentration is used for dilute or concentrate sprays. Dilute application rate is based on typical 2,000 L/ha spray volume. Repeat applications at 10-14 day intervals. Recommended tank mix with a protectant fungicide.[4]
Score® Top 20 WG (Germany)	Foliar; Broadcast; Equipment type not specified	0.047 (52.5) [5]	4	0.187 (210)	28	Approved quantity of water for application is specified at 500 l/ha per 1 m crown height; RTI of 6-10 days.
Score® Top 20 WG (Switzerland)	Foliar; Broadcast; Equip type not specified	0.050 (56) [6]	4	0.200 (224)	21	Applications may be made alone or to increase security protection tank mix with a contact fungicide such as Delan 500 SC (dithianon) or captan; RTIs are dependent on weather conditions and new growth, or 12-14 days.
Sweet/Pop Corn						
Dividend® 3FS	Seed-treatment slurry	30 g ai/100 kg seed, or 1.05 oz. ai/100 lb seed	NA	30 g ai/100 kg seed, or 1.05 oz. ai/100 lb seed		
Cotton						
Dividend® 3FS	Seed-treatment slurry	35 g ai/100 kg seed, or 1.23 oz. ai/100 lb seed	NA	35 g ai/100 kg seed, or 1.23 oz. ai/100 lb seed		

[1] Application rates based on acreage were not available from the labels; the actual rates were presented under MRID 44785102 (summary of pome fruit residue data) or MRID 44785101 (summary of grape residue data), based on typical volumes applied per hectare.

[2] Maximum seasonal rates were not specified on the labels, but provided in a table under MRID 44785102 (summary of pome fruit residue data) or MRID 44785101 (summary of grape residue data).

[3] May be mixed with Chorus®, Supracide®, Insegar®, Pyranica®, Delfin®, Dipel*, Mavrik®, Pirimor*, and some formulations of chlorpyrifos, diazinon, azinphos-methyl, parathion, propargite, carbaryl, endosulfan, calcium nitrate, calcium chloride, magnesium sulphate and the protectant scab fungicides mancozeb, dithianon, metiram, and ziram.

[4] Compatible with most commonly used insecticides and fungicides, except oil and strongly alkaline materials such as Bordeaux mixture and lime sulphur.

[5] Difenoconazole rates; this product is a MAI and the penoconazole application rate is 0.020 lb ai/A (22.5 g ai/ha).

[6] Difenoconazole rates; this product is a MAI and the penoconazole application rate is 0.021 lb ai/A (24 g ai/ha).

Conclusions: Label revisions are requested for the French and Swiss version of the product label for Score® 250 EC/Slick® 250 EC to specify a PHI for grapes; the available data would support a

55-day PHI.

4.3 Dietary Exposure/Risk Pathway

Nature of the Residue - Plants/Livestock: No plant or livestock metabolism studies were submitted with the subject petitions. However, the qualitative nature of the residues in plants and livestock is adequately understood, based on adequate canola (foliar), grape (foliar), potato (foliar), tomato (foliar), wheat (foliar and seed-treatment), goat and hen metabolism studies submitted with previous difenoconazole petitions. The HED Metabolism Assessment Review Committee (MARC) has determined that for tolerance expression and risk assessment purposes, the residue of concern is difenoconazole *per se* for plant and livestock commodities. For the purposes of this action only, the alcohol metabolite (CGA-205375) does not need to be regulated. The MARC, however, stated that if tolerances are proposed for difenoconazole resulting from foliar uses which result in higher residue levels of CGA-205375 than parent, then the need to include CGA-205375 should be reconsidered. If CGA-205375 is included in the tolerance expression, then new analytical enforcement methodology and a second lab validation will be required. If quantifiable levels of residues are found in livestock feed items, then livestock feeding studies will be required (Memo, G. Kramer, 22-JUL-1994; No DP#).

Residue Analytical Enforcement Methods: Adequate residue analytical methods are available for tolerance enforcement. Method AG-575B, the current enforcement method for plant commodities, quantitates levels of difenoconazole by gas chromatography (GC) with nitrogen/phosphorous (N/P) detection; the limit of quantitation (LOQ) is 0.05 ppm for difenoconazole residues. Method AG-544, the current enforcement method for livestock commodities, also quantitates levels of difenoconazole by GC with N/P detection; the LOQs for difenoconazole residues are 0.05 ppm in meat and eggs and 0.01 ppm in milk. A GC/mass-spectrometry detection (MSD) method for the confirmation of difenoconazole residues in/on canola seed has recently undergone petition method validation (PMV) at EPA's Analytical Chemistry Lab (ACL). The confirmatory method has been determined to be suitable for tolerance enforcement once the revisions recommended by ACL are incorporated.

Several residue analytical methods were used to quantitate residues of difenoconazole in/on samples collected from the residue field and processing studies on grapes and pome fruits. These methods, which include Methods RES 04/89, RES 10/93, RES 14/93, AG-514, and REM 7/86, are earlier versions of the current enforcement Method AG-575B. These methods are adequate for data collection based on validation data as well as concurrent method recoveries reported in the individual studies.

Magnitude of the Residue - Plants: The following paragraphs are summaries of the barley, pome fruit, grape, sweet/pop corn, and cotton residue data submitted in support of these requests.

Barley: A tolerance is established for imported barley grain under 40 CFR § 180.475(a). Tolerances were proposed (PP# 6F04748) for barley forage, straw, and hay; however, several deficiencies were noted (Memo, G. Kramer, 24-JAN-1997; DP# 232351). All deficiencies have since been resolved and the data support the proposed tolerances (Memo, G. Kramer, 13-APR-2005; DP# 238550).

Pome Fruit: The petition package provides information which states that difenoconazole is currently registered for foliar uses on pome fruits in Australia, France, New Zealand, South Africa, and Switzerland. It is also proposed for registration in Chile and Germany. In support of this tolerance petition, Syngenta has conducted pome fruit trials in Australia, Chile, Germany, New Zealand, South Africa, and Switzerland. In addition, supplemental trials were also conducted in Brazil. Although the majority of the submitted residue data for apples and pears, from trials conducted in Australia, Chile, Germany, New Zealand, South Africa, and Switzerland, reflect slightly exaggerated seasonal rates for each country, they are nonetheless adequate to support a tolerance of 0.10 ppm for imported pome fruits. The petitioner is requested to submit a revised Section F to revise commodity definition from "Pome Fruit" to "Fruit, pome, group 11."

The maximum residues of difenoconazole in/on apples, from field trials reflecting the label PHI and slightly exaggerated seasonal rate for each country, are as follows: (i) Australia - 0.09 ppm in/on samples harvested 28 days following the last of multiple foliar applications at 0.8-1.5x the maximum label seasonal rate; (ii) Chile - 0.07 ppm in/on samples harvested 27/28 days following the last of multiple foliar applications at 1.4-1.5x; (iii) Germany - 0.06 ppm in/on samples harvested 28 days following the last of multiple foliar applications at 1.4-1.5x; (iv) New Zealand - 0.07 ppm in/on samples harvested 35/36 days following the last of multiple foliar applications at 1x; (v) South Africa - 0.10 ppm in/on samples harvested 14 days following the last of multiple foliar applications at 1.2x; and (vi) Switzerland - 0.11 ppm in/on samples harvested 21 days following the last of multiple foliar applications at 1.4x.

The maximum residues of difenoconazole in/on pears, from field trials reflecting the label PHI and maximum seasonal rate for each country, are as follows: (i) Australia - 0.04 ppm in/on samples harvested 28 days following the last of multiple foliar applications at 1x; (ii) Chile - 0.07 ppm in/on samples harvested 28 days following the last of multiple foliar applications at 1.4-1.5x; and (iii) Germany - 0.101 ppm in/on samples harvested 29 days following the last of multiple foliar applications at 1.5x.

Grape: The petition package includes information which states that difenoconazole is currently registered for foliar uses on grapes in France and Switzerland, and proposed for registration in Chile and South Africa. In support of this tolerance petition, Syngenta has conducted grape field trials in Chile, France, and South Africa. In addition, supplemental trials were conducted in Italy and Spain. The submitted residue data for imported grapes, from trials conducted in Chile and France, indicate that a tolerance of 0.10 ppm will not be exceeded when the proposed formulation is applied according to the maximum label use directions for each country. Additional data, from grape trials conducted in Italy, Spain, and South Africa, should be considered supplemental because the rates used in the trials were either <1x or exaggerated.

The maximum residues of difenoconazole in/on grapes, from field trials reflecting the maximum label use pattern for each country, are as follows: (i) Chile - 0.05 ppm in/on samples harvested 59-63 days following the last of three broadcast foliar applications at 1x the maximum label seasonal rate; and (ii) France - 0.02 ppm (1995 trials) and 0.05 ppm (1992 trials) in/on samples harvested 55-90 days following the last of four broadcast foliar applications at 1x. A PHI for grape is not listed on the difenoconazole end-use product registered in France and Switzerland.

Based on these data, HED recommends that the French and Swiss version of the product label for Score® 250 EC/Slick® 250 EC be amended to specify a PHI for grapes; the available data would support a 55-day PHI.

Sweet/Pop Corn: Syngenta has submitted field trial data for difenoconazole on sweet corn and popcorn. A total of nine sweet corn field trials were conducted in CA (1), FL (1), MN (1), NC (1), NY (1), OH (1), OR (1), WA (1), and WS (1) and three popcorn field trials were conducted in IN (1), KS (1), and ND (1) during the 1998 growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500. Dividend® 3FS contains 3 lb difenoconazole/gal of formulated product. The total rate applied to seed was 30 g ai/100 kg seed (1.05 oz. ai/100 lb seed; 1x maximum application rate). Sweet corn forage with ears were harvested at 38-81-day PHI, sweet corn forage without ears were harvested at a 60-102-day PHI, sweet corn kernel + cob with husks removed (K+CHR) were harvested at a 60-131-day PHI, and sweet corn stover were harvested at a 80-151-day PHI. Popcorn grain and stover were both harvested at 129-144-day PHIs. Residues of difenoconazole from the study use pattern did not exceed the LOQ (<0.01 ppm for sweet corn and pop corn); therefore, there is no expectation of quantifiable residues at the proposed use rate. The residue data thus support the proposed tolerances.

Cotton: Syngenta has submitted field trial data for difenoconazole on cotton. A total of nine cotton field trials were conducted in AL (1), AZ (1), CA (1), LA (1), MS (1), NM (1), OK (1), and TX (2) during the 1996 growing season. The number and locations of field trials are in accordance with OPPTS Guideline 860.1500. Dividend® 3FS is a flowable-slurry formulation that contains 3 lb difenoconazole/gal of formulated product. The total rate applied to seed was 35 g a.i./100 kg (1.23 oz. ai/100 lb seed; 1x maximum application rate). Cotton undelinted seed and gin byproduct samples were harvested at a 132-189-day PHI. Residues of difenoconazole from the study use pattern did not exceed the LOQ (<0.05 ppm for undelinted seed and gin byproduct); therefore, there is no expectation of quantifiable residues at the proposed use rate. The residue data thus support the proposed tolerances.

Magnitude of the Residue - Livestock: The proposed uses in this action do not lead to higher residues of concern in milk and meat of ruminants or poultry. The currently-established difenoconazole tolerances for milk, eggs, fat, meat, and meat byproducts of cattle, goat, hog, horse, poultry, and sheep are adequate for the purpose of this action only. However, a dairy cattle feeding study will be needed for any future tolerance request on potential livestock feed commodities which could lead to higher residues of concern in meat and milk or if quantifiable levels of metabolite CGA-205375 residues are found in livestock feed items.

Processed Food and Feed: The following paragraphs are summaries of the apple, grape, and cotton processing data submitted in support of these requests.

Apple: A total of 20 apple processing studies were submitted in support of this action. When all studies are considered *in toto*, they are adequate to support the proposed uses on apples pending submission of confirmatory storage stability data for apple juice and wet pomace. These studies all show that residues of difenoconazole do not concentrate in juice; thus, a tolerance for apple juice is not needed. The studies also indicate that residues of difenoconazole concentrate in wet

pomace with processing factors ranging from 1.9x to 7x. When the processing factors observed in wet pomace are averaged to include only those processing studies which resulted in quantifiable residues in the raw agricultural commodity (RAC), the overall average processing factor is 3.9x. The highest-average field trial (HAFT) residues observed in the apple field trials were 0.05 ppm in Australia, 0.07 ppm in Chile, 0.06 ppm in Germany, 0.07 ppm in New Zealand, and 0.10 ppm in South Africa. Based on an overall average processing factor of 3.9x and a HAFT residue of 0.10 ppm, the expected residues in apple pomace following (or approximating) treatment at 1x would be 0.39 ppm. However, wet apple pomace is not imported; therefore, a tolerance is not necessary. The petitioner is requested to submit a revised Section F to delete the proposed tolerance on imported wet apple pomace.

Grape: A total of 24 grape processing studies were submitted in support of this action. When all studies are considered *in toto*, they are deemed adequate to support the proposed uses on grapes pending submission of confirmatory storage stability data for grape juice and raisins. Processing studies conducted in Chile and France indicate that residues of difenoconazole do not concentrate in juice; therefore, a tolerance for grape juice is not needed.

In its initial data package submission, Syngenta did not submit raisin data although a tolerance of 0.5 ppm is proposed in the current petition. The proposed tolerance level was based on theoretical calculation of expected residues multiplied by the expected concentration factor for raisins. From the Pesticide Analytical Manual, Volume I, Section 201, grapes contain an average of 80.93% moisture and raisins contain an average of 15.65%, resulting in a concentration factor of 5.2x.

A later submission (MRID 45592401) contained raisin data from processing studies conducted in Chile. One of these studies indicate that residues of difenoconazole marginally concentrated in raisin (processing factors of 1.2-1.4x; average of 1.3x). The HAFT residues observed in the grape field trials were 0.04 ppm in Chile, 0.05 ppm in France, and 0.06 ppm in Spain. Based on an average processing factor of 1.3x and a HAFT residue of 0.06 ppm, the expected residues in raisins following treatment at 1x would be 0.078 ppm. Because the expected residues do not exceed the recommended tolerance of 0.10 ppm for grape (RAC), a tolerance for raisin is not needed. Syngenta is requested to submit a revised Section F to delete the proposed tolerance on imported raisins.

Cotton: Two cotton processing studies were conducted in CA (n=1) and TX (n=1). Dividend® 3FS contains 3 lb difenoconazole/gal of formulated product. The total rate applied to seed was 105 g ai/100 kg seed (3.7 oz. ai/100 lb seed). At each trial location, undelinted cotton seed (the RAC) was harvested 189 or 165 days after planting, respectively. Undelinted cotton seed was processed into hulls, meal, or refined oil (the significant processed commodities of cotton according to OPPTS 860.1000, Table 1). Residues of difenoconazole were below the method LOQ (<0.05 ppm) in/on all untreated (control) samples of cotton. The results of the processing studies from both trials indicate that difenoconazole residues were less than the method LOQ in all undelinted seed (RAC) and processed samples, harvested 165-189 days after planting. Because the RAC and processed commodities were all <LOQ, processing factors were not calculated. The cotton processing study was deemed adequate to support the proposed use on cotton. Processing study indicates that residues of difenoconazole do not concentrate in hulls,

meal, or oil; therefore, separate tolerances are not needed.

Storage Stability Data: The available storage stability data (cotton, potato, tomato, and wheat for up to two years) may be translated to validate the storage intervals of samples collected from the grape, pome fruit, cotton, and sweet corn and pop corn residue field trials. However, the available storage stability data for processed plant commodities are marginal; therefore, storage stability data on the processed commodities of apples (wet pomace and juice) and grapes (raisin and juice) are requested for this action. The requested storage stability data should reflect the longest storage intervals reported in the processing studies (*i.e.*, 17.5 months for apples, 14.2 months for grape juice and 4.2 months for raisins).

Tolerance Summary: There are currently no established Codex, Canadian, or Mexican maximum residue limits (MRLs) for difenoconazole. An International Residue Limit Status (IRLS) sheet is attached to this review. Pending submissions of confirmatory storage stability data and revised Sections B and F, the available crop field trial data will support the establishment of tolerances for residues of difenoconazole *per se* in/on imported grape, pome fruit, and apple pomace. The proposed tolerance of 0.5 ppm in/on raisins is not needed because the expected residues of difenoconazole in raisins are not likely to exceed the proposed tolerance of 0.1 ppm for grape (RAC) when the proposed formulation(s) are applied according to maximum label use pattern. Furthermore, the proposed tolerance of 0.4 ppm in/on wet apple pomace is not needed because it is not imported into the U.S. Below in Table 4 is the proposed and HED-recommended tolerance summary for difenoconazole.

Table 4. Tolerance Summary for Difenoconazole.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments/ *Correct Commodity Definition*
Grapes	0.1	0.10	*Grape*
Pome Fruit	0.1	0.10	*Fruit, pome, group 11*
Raisins	0.5	Not needed	
Wet Apple Pomace	0.4	Not needed	
Barley, hay	0.05	0.05	
Barley, straw	0.05	0.05	
Barley, forage	0.05	0.05	
Cotton, undelinted seed	0.05	0.05	
Cotton, gin byproducts	0.05	0.05	
Corn, sweet, forage	0.01	0.01	
Corn, sweet, stover	0.01	0.01	
Corn, sweet, kernel plus cob with husks removed	0.01	0.01	

4.4 Water Exposure and Risk Pathway

The following information concerning the environmental fate and drinking water assessment of difenoconazole was provided by EFED (Memo, M. Janson, *et al.*, 06-MAY-2005; DP# 307166). At the present time, surface and ground water monitoring data are not available for difenoconazole.

Ground and Surface Water EDWCs: The drinking water residue of concern for risk assessment purposes was decided by the difenoconazole risk assessment team (Memo, S. Levy, *et al.*, 23-NOV-1999; DP# 258774). Drinking water estimates include surface water EDWCs based on the FIRST model (version 1.0) and the SCI-GROW groundwater regression model (version 2.3), which was developed from studies with different hydrology and study conditions. Both models assumed a treatment rate for difenoconazole on wheat seed of 0.0245 lbs. a.i./ 100 lbs of seed (based on EPA Reg. No. 100-740) and a maximum seeding rate of 180 lbs. wheat seed/acre. Therefore, the maximum difenoconazole application rate used was 0.044 lbs ai/acre. The EDWCs estimates are as follows:

ground water estimate:	0.00084 ppb (acute and chronic)
surface water estimate:	0.60 ppb; peak concentration 0.14 ppb; average annual

EFED noted that the models used are not specifically designed to estimate concentrations for pesticides used for seed treatment; therefore, there are uncertainties in their predictive potential. However, these uncertainties are not expected to substantially decrease the conservativeness of the Tier 1 modeling results (see EFED memorandum cited above for more details).

4.5 Dietary-Exposure Analysis

Acute and chronic dietary risk assessments were conducted using the DEEM-FCID™ (ver. 2.03) model which uses food consumption data from the USDA's CSFII from 1994-1996 and 1998. A cancer dietary assessment was not conducted for difenoconazole because the cancer NOAEL is higher than the chronic RfD (4.7 mg/kg/day vs. 0.96 mg/kg/day, respectively); therefore, the chronic dietary risk estimate is more protective.

The acute analysis assumed tolerance-level residues, 100% CT, and DEEM™ (ver. 7.76) default processing factors for all proposed and registered commodities (Tier 1). The chronic analysis assumed tolerance-level residues for all proposed commodities, ARs for the previously-registered commodities, and 100% CT and DEEM™ (ver. 7.76) default processing factors for all commodities (partially refined, Tier 2 analyses). Drinking water was incorporated directly in the dietary assessment using the peak concentration for the acute dietary and the average annual concentration for the chronic dietary assessments. The resulting acute and chronic dietary risk estimates (food + water) were less than HED's levels of concern (<100% aPAD and <100% cPAD, respectively; see Table 5).

Table 5. Summary of Dietary Exposure and Risk for Difenoconazole.

Population Subgroup	Acute Dietary		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	NA	NA	0.000240	2.4
All Infants (< 1 year old)			0.001004	10
Children 1-2 years old			**0.001558**	**16**
Children 3-5 years old			0.000933	9.3
Children 6-12 years old			0.000330	3.3
Youth 13-19 years old			0.000126	1.3
Females 13-49 years old	**0.001502**	**<1.0**	0.000121	1.2
Adults 20-49 years old	NA	NA	0.000120	1.2
Adults 50+ years old			0.000126	1.3

4.6 Residential Exposure and Risk Pathway

There are not registered or proposed uses of difenoconazole that would result in residential exposure.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

Including all existing and proposed uses, human-health risk assessments have been conducted for the following exposure scenarios: acute and chronic dietary exposures (food + water only). **All aggregate exposure and risk estimates are below HED's level of concern.** Because there are no uses of difenoconazole that could result in residential exposures, this aggregate risk assessment takes into consideration dietary food + water exposure only; therefore, the acute and chronic aggregate estimates would be the same as the dietary exposure results shown in Table 5 above.

6.0 CUMULATIVE RISK

The Agency did not perform a cumulative risk assessment as part of this tolerance action for difenoconazole. However, the Agency does have concern about potential toxicity to 1,2,4-triazole and two conjugates, triazolylalanine and triazolyl acetic acid, metabolites common to most of the triazole fungicides. To support the extension of existing parent triazole-derivative fungicide tolerances, EPA conducted an interim human health assessment for aggregate exposure to 1,2,4-triazole (M. A. Doherty, "Interim Human Health Risk Assessment of 1,2,4-Triazole to Support Tolerance Extensions and New Section 18 Soybean Tolerances for Triazole-Derivative Fungicides," 29-JUN-2004, DP# 304288). The exposure and risk estimates presented in this assessment are overestimates of actual likely exposures and therefore, should be considered to be highly conservative. Based on this assessment the EPA concluded that for all exposure durations

and population subgroups, aggregate exposures to 1,2,4-triazole are not expected to exceed its level of concern. This assessment should be considered interim due to the ongoing series of studies being conducted by the U.S. Triazole Task Force (USTTF). Those studies are designed to provide the Agency with more complete toxicological and residue information for free triazole and are expected to be submitted to the Agency. Upon completion of review of these data, EPA will prepare a more sophisticated assessment based on the revised toxicological and exposure databases.

7.0 OCCUPATIONAL EXPOSURE

7.1 Handler Exposure

Based on the proposed use pattern and HED's previous experience with seed treatment and seed treatment materials, HED believes the most highly exposed occupational pesticide handlers in this case are: 1) mixer/operator, 2) bagger and 3) bag sewer. In this regard, Syngenta submitted "An Evaluation of Exposure to Mixer/Operators, Baggers, and Bag Sewers Handling the Active Ingredient Difenoconazole (Dividend® Twin-Pak™ FUNGICIDE) During Cotton Seed Treatment" (MRID 44490801). Syngenta based its assessment on MRID 430800049 "Worker Exposure to Apron Flowable While Treating Seed Commercially." The Syngenta assessment was based on the maximum application rate for cotton (1.25 fl oz/cwt) and toxicological endpoints from a 1995 memorandum by B. Kitchens ("Evaluate New Use of on Farm Seed Treatment for the Active Ingredient Difenoconazole (Dividend 0.15 and 0.31 FS) and Conduct an Exposure Assessment"). Syngenta assumed 100% dermal absorption.

On 08-SEP-1998, the HED HIARC identified a short-term (1-7 days) dermal toxicological endpoint (25 mg a.i./kg bw/day) from a developmental study in the rabbit and an intermediate-term dermal toxicological endpoint (1.25 mg a.i./kg bw/day) from a 2-generation reproduction study in the rat. The HIARC determined that a 75% dermal-absorption factor should be used since the dermal endpoints were determined from oral studies.

The RAB1 chemical review team has determined that the original determination of short-term duration exposures (1-7 days) is applicable to HED's current policy of considering short-term exposure duration as being 1-30 days. The original HIARC review did not include inhalation toxicological endpoints. The RAB1 chemical review team has determined that inhalation exposure and risk assessment is necessary and that the short-term and intermediate-term duration inhalation exposures should be assessed using the same toxicological endpoints as were determined for dermal exposures. For inhalation exposure, HED assumes 100% absorption.

The CPRC has classified difenoconazole as a Group C possible human carcinogen. The Committee recommended using the MOE approach for assessment (Memo, J. Rowland and E. Rinde, 27-JUL-1994). Handler exposures are not expected to be chronic exposures; therefore, a cancer risk assessment is not necessary for this action.

The HED Science Policy Council for Exposure (ExpoSAC) in conjunction with the Gustoffsen seed treatment company has developed software to facilitate estimation of exposure and risk that result from commercial seed treatment. The software uses HED standard computational

practices in conjunction with "unit exposures" derived from a number of seed treatment studies evaluated and accepted by HED. Unit exposures are expressed as mg ai/lb ai handled and are specific to "job" or work activity.

The results from the seed treatment calculator are presented in the following tables, for short- and intermediate-term exposures for each proposed crop seed. The calculator uses the following convention.

a) Label Rate (fl oz/cwt) x concentration (lb ai/gal) ÷ 128 fl oz/gal ÷ 100
b) Unit Exposure (UE) from Standard Operating Procedure for seed treatment (Guidance No. 14, May 1, 2003.
c) Daily Exposure (loaders, sewers, bagger & multiple activities =
[Rate (lb ai/lb seed) x amt seed treated/day x % absorption x UE (mg ai/lb handled) ÷ body weight]
d) Daily Exposure (seed planters) = [Rate (lb ai/lb seed) x lb seed planted/day x % absorption x UE ÷ body weight
e) MOE (unitless) = toxicological endpoint (mg a.i./kg bw/day) ÷ daily exposure (mg a.i./kg bw/day)
f) Combined MOE (unitless) 1/(1/Dermal MOE) + (1/Inhalation MOE)

ESTIMATES OF OCCUPATIONAL PESTICIDE HANDLER EXPOSURE TO DIFENOCONAZOLE FROM COMMERCIAL SEED TREATMENT

Table 6. Calculate Handler Exposure and MOE.

Barley Short-Term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short-Term MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader/Applicator:	0.0230	0.00034	0.043266	0.000853	578	29316	570
Sewer:	0.0062	0.00023	0.011663	0.000577	2144	43336	2000
Bagger:	0.0091	0.00016	0.017118	0.000401	1460	62296	1400
Multiple Activities:	0.0420	0.00160	0.079008	0.004013	316	6230	300
Seed Planters:	0.2500	0.00340	0.012445	0.000226	2009	110783	2000

Table 7. Calculate Handler Exposure and MOE.

Barley Intermediate-Term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Intermediate-Term MOE [c]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader/Applicator:	0.0230	0.00034	0.043266	0.000853	29	1466	28
Sewer:	0.0062	0.00023	0.011663	0.000577	107	2167	100
Bagger:	0.0091	0.00016	0.017118	0.000401	73	3115	71
Multiple Activities:	0.0420	0.00160	0.079008	0.004013	16	311	15
Seed Planters:	0.2500	0.00340	0.012445	0.000226	100	5539	99

Table 8. Calculate Handler Exposure and MOE.

Cotton Short-Term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short-Term MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader/Applicator:	0.0230	0.00034	0.012052	0.000238	2074	105243	2000
Sewer:	0.0062	0.00023	0.003249	0.000161	7695	155577	7300
Bagger:	0.0091	0.00016	0.004768	0.000112	5243	223642	5100
Multiple Activities:	0.0420	0.00160	0.022008	0.001118	1136	22364	1100
Seed Planters:	0.2500	0.00340	0.002947	0.000053	8482	467748	8300

Table 9. Calculate Handler Exposure and MOE.

Cotton Intermediate-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Intermediate-Term MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader/Applicator:	0.0230	0.00034	0.012052	0.000238	104	5262	100
Sewer:	0.0062	0.00023	0.003249	0.000161	385	7779	370
Bagger:	0.0091	0.00016	0.004768	0.000112	262	11182	260
Multiple Activities:	0.0420	0.00160	0.022008	0.001118	57	1118	54
Seed Planters:	0.2500	0.00340	0.002947	0.000053	424	23387	420

Table 10. Calculated Handler Exposure and MOE.

Sweet Corn Short-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Short-Term MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader/Applicator:	0.0230	0.00034	0.011690	0.000230	2139	108498	2100
Sewer:	0.0062	0.00023	0.003151	0.000156	7933	160389	7600
Bagger:	0.0091	0.00016	0.004625	0.000108	5405	230559	5300
Multiple Activities:	0.0420	0.00160	0.021348	0.001084	1171	23056	1100
Seed Planters:	0.2500	0.00340	0.001965	0.000036	12723	701623	12000

Table 11. Calculated Handler Exposure and MOE.

Sweet Corn Intermediate-term	Unit Exposure (UE) mg/lbs.ai [b]		Daily Exposure mg/kg/day [c, d]		Intermediate-Term MOE [e]		Combined MOE [f]
	Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation	Dermal & Inhalation
Loader/Applicator:	0.0230	0.00034	0.011690	0.000230	107	5425	100
Sewer:	0.0062	0.00023	0.003151	0.000156	397	8019	380
Bagger:	0.0091	0.00016	0.004625	0.000108	270	11528	260
Multiple Activities:	0.0420	0.00160	0.021348	0.001084	59	1153	56
Seed Planters:	0.2500	0.00340	0.001965	0.000036	636	35081	620

For short-term exposures, all MOEs are >100 and the risks do not exceed HED's level of concern. For intermediate-term duration dermal exposures (1-6 months), some MOEs are < 100.

For barley:	loader/applicator	MOE 29
	bagger	MOE 73
	multiple activities	MOE 16 (multiple activities are comprised of "odd jobs" such as sweeping/cleaning up at day's end);
For cotton:	multiple activities	MOE 57
For sweet corn:	multiple activities	MOE 59

In order to reduce dermal exposure, workers could be asked to wear additional protective clothing such as coveralls over normal work clothing. However, seed treatment facilities are often very hot during summer months and an additional layer would likely prove more of a problem from heat stress. HED notes that the estimates are based on a 75% dermal-absorption factor that is derived from an oral study. A 75% dermal-absorption factor should be viewed as highly conservative, *i.e.*, protective. HED believes it is unlikely that an individual would actually experience intermediate-term exposures. That is to say, it is unlikely that an individual would treat either of the three grains, uninterrupted, for a period of 1-6 months. Seed treaters are likely to receive orders for treatment with other materials etc such that it is more likely that a series of short-term duration (1-30 days) exposures might occur. Due to the conservative nature of the assessment and the uncertainties involved in the dermal-absorption factor, HED does not recommend additional protective factors in this situation.

Based on conservative inputs and the expected use patterns, HED does not have any concerns for workers from post-application exposure.

7.2 Post-Application Worker Exposure

HED has assessed growers who are planting treated seed and the MOEs were found to be acceptable (handler exposure). Since seed is covered with soil after the seed is planted, there is no postapplication exposure to assess for this action.

7.3 REI

Since the proposed use pattern is for treatment of seed, a REI for the proposed uses is not applicable. The label does list a REI of 12 hours for re-entering fields planted with treated seed. Difenoconazole is classified in Acute Toxicity Category III for acute dermal toxicity and primary eye irritation. It is classified in Category IV for acute inhalation toxicity and primary skin irritation. It is not a dermal sensitizer. Therefore, the interim worker protection standard (WPS) REI of 12 hours is adequate to protect workers who might enter fields planted with treated seed.

8.0 DEFICIENCIES/DATA NEEDS

8.1 Toxicology

- None

8.2 Chemistry

- Storage stability data on the processed commodities of apples (wet pomace and juice) and grapes (raisin and juice) are requested. The requested storage stability data should reflect the longest storage intervals reported in the respective processing studies (*i.e.*, 17.5 months for apples, 14.2 months for grape juice and 4.2 months for raisins).

- The French and Swiss version of the product label for Score® 250 EC/Slick® 250 EC should be amended to specify a PHI for grapes; the available data would support a 55-day PHI.

- The confirmatory method has been determined to be suitable for tolerance enforcement once the revisions recommended by ACL are incorporated.

- A revised Section F should be submitted with the following correct commodity definition: "Pome Fruit" to "Fruit, pome, group 11." In addition, the proposed tolerance on raisin and wet apple pomace should be deleted.

8.3 Occupational/Residential

- None

cc: S. Levy (RAB1), G. Reddy (RAB1), M. Dow (RAB1)
RDI: RAB1 Branch (27-JUL-2005), G.F. Kramer (04-AUG-2005)
S. Levy: 806T: CM#2: (703) 305-0783: 7509C: RAB1

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